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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0117
International Conference on Harmonization; Draft Guidance on E2E Pharmacovigilance Planning

Dear Sir/Madam:

GlaxoSmithKline (GSK) is a research-based pharmaceutical company engaged in the discovery, development, manufacture, and sale of prescription and over-the-counter pharmaceutical products and vaccines. We appreciate the opportunity to provide comments on the ICH draft guidance on pharmacovigilance planning.

In general, GSK supports the concepts outlined in the guidance document, and congratulates the ICH E2E Expert Working Group on developing a clear and comprehensive document. We are also encouraged to see that the concepts outlined in the draft guidance appear to be consistent with those contained in previous FDA and EU documents related to risk management. However, we believe that clarifying the wording in several sections would enhance the document's usefulness. Our comments and suggestions for revisions are attached.

Sincerely,

Edward N. Pattishall, MD, MPH
Vice President
Global Clinical Safety & Pharmacovigilance

2004D-0117

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General Comments

Identified and potential risks: The second paragraph of the Scope section introduces the terms/concepts of "identified risks" and "potential risks", which are used throughout the document. The term "identified risks" implies an established causal relationship to the drug product, while "potential risks" could represent either situations where events have been reported but causality remains a question, or an anticipated risk based on experience with other drugs in the same class or the drug's pharmacology. While we understand the general concept behind creating two terms, in practice, we find it difficult to distinguish a point where a potential risk would become an identified risk. While this is not so much an issue when the terms are used in the Scope section of the guideline, it is more of an issue with regard to the Pharmacovigilance Specifications and Plans, which require separate discussions of important identified risks and important potential risks. The Pharmacovigilance Specification should be evidence-based, and the events that have been reported should be characterized to the fullest extent possible. We propose that the Pharmacovigilance Specification describe the "potential risks of interest" or "suspected risks", and characterize the nature of those risks including seriousness, frequency, predictability, reversibility, and whether the events are preventable (e.g., drug-drug interactions) or idiosyncratic.

If this is not possible, we suggest that definitions of "identified" and "potential" risk be developed, and incorporated into the document.

Definitions: Although the guidance document does include a definition for pharmacovigilance, consideration should be given to expanding the list of defined terms, and to including a "Definitions" section in the guidance document. This would serve to eliminate confusion and divergent interpretations of terms used throughout the document. Suggestions for additional terms that should be defined include:

- "early postmarketing period" (suggest that this be the first three years of marketing, consistent with FDA's peri-approval period)
- serious (this could be the definition in the ICH E2A guidance)
- frequent
- identified risks (if not changed as described above)
- potential risks (if not changed as described above)

Specific Comments

Section 1.3 Scope

As drafted, the guideline would apply to "...significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process of a biotechnology-derived product) and.... new populations or in significant new indications." This would require a sponsor to produce a Pharmacovigilance Specification and Pharmacovigilance Plan for nearly any change to an existing product. Many product line extensions do not substantially impact the benefit/risk profile of a drug/biologic, and should not warrant creation of Pharmacovigilance Specifications and Plans. We suggest that the first paragraph in this section be reworded to read:

> The guideline could be most useful for new chemical entities and biotechnology-derived products. It is also useful for applications to support a major new use or indication for established products (e.g., new population). The need for a Pharmacovigilance Specification and Pharmacovigilance Plan for other situations (e.g., new dosage form) should be assessed on a case by case basis.

The third paragraph indicates that the Pharmacovigilance Specification and Pharmacovigilance Plan could be included in the Common Technical Document (CTD). We suggest that this section include specific direction regarding the location of this information (e.g., Module 1 of the CTD).

In the fourth paragraph, we request that the word "might" be changed to "should", so that this sentence reads:

> For products for which no special concerns have arisen, routine pharmacovigilance activities should be considered adequate for the Pharmacovigilance Plan.

As noted in Section 1.2. Background, the decision to approve a drug is based on a satisfactory balance of benefits and risks, and once the product is marketed, emerging information can have an impact on benefits or risks, thus changing this balance. For this reason, we suggest that the fifth paragraph in the Scope section be revised to include the concept of ongoing review of benefits as well as risks, as follows:

> During the course of implementing the various components of the plan, any important emerging benefit or risk information should be discussed and used to revise the plan.

Section 2 Pharmacovigilance Specification

In line with our general comments above regarding identified and potential risks, we suggest that the first paragraph be reworded as follows:

> The Pharmacovigilance Specification is a summary of the suspected risks of a drug, the populations potentially at-risk, and outstanding safety questions that should not delay approval, but which warrant further investigation to refine understanding of the benefit risk profile. This Pharmacovigilance Specification is intended to help industry and regulators identify any need for specific data collection in the post-approval period and also to facilitate the construction of the Pharmacovigilance Plan.

2.1. Elements of the specification

The second paragraph in this section states that the "focus of the Pharmacovigilance Specification should be on...important missing information." We suggest that the term "missing information" be replaced with "further evidence required" in this section and throughout the document. In addition, we suggest that wording in this section be clarified to specify that this refers to important information that is relevant to the proper use of the drug product. Although understanding of both the potential benefits and risks of a product continue to evolve following market introduction, only specific outstanding questions related to product safety are relevant to the Pharmacovigilance Specification.

2.1.1. Non-clinical

The first sentence could be clarified by restating it as follows:

> Within the Specification, this section should present safety concerns raised by findings of non-clinical studies that have not been resolved by clinical data, for example:

2.1.2.b. Populations not studied in the pre-approval phase

The beginning of this section could be expanded to read:

> The specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-approval phase. It should describe outstanding

questions to be addressed by post-approval studies to gain a better understanding of the benefits and risks of the product in clinical practice. Information on populations not studied in clinical trials (e.g., disease severity or patients with specific underlying medical conditions) should also be included, especially if the product is not contraindicated in these populations, or where experience is limited. Populations to be considered should include (but might not be limited to):

2.1.2.c. Adverse events (AEs)/Adverse drug reactions (ADRs)

In the section on "Safety issues that require further evaluation", we suggest adding "reversibility" to the list of factors that might have an impact on the balance of benefits and risks of the product.

If the guidance document continues to classify risks as "identified" and "potential" risks, the section on "Potential risks that require further evaluation" should be revised to specify that the "potential risks" are based on evidence/fact, and not merely conjecture or hypothetical situations. The same comment applies to the following section 2.1.2.d., "Identified and potential interactions, including food-drug and drug-drug interactions".

2.1.2.e. Epidemiology of the indication(s) and important adverse events

It is unclear whether the "epidemiology of ...important adverse events in the target population" refers to the occurrence of comorbid conditions, which might be mistaken for adverse events, or whether the suggestion to include such information would be broadening the statement. Our epidemiologists have long thought that an understanding of comorbidities in the patient population that is likely to use the drug is potentially very helpful in interpreting some safety issues (e.g., from spontaneous reports) that arise in the peri-approval period. In the case where the drug does not represent a new class of compounds, a review of the frequency of AEs in already marketed drugs in the class is also very helpful. Risk factors for such events in addition to measures of frequency would also be critical to understand and review.

New drugs are frequently prescribed to more severely ill patients, and the nature of this potential "selective prescribing" should be discussed and strategies for interpretation of the post-marketing pharmacovigilance detail should be outlined if possible.

2.2. Summary

See previous comments regarding identified and potential risks. In addition, we suggest that the "important missing information" bullet be revised to read:

- Outstanding questions to be assessed in the post-marketing setting

Section 3 Pharmacovigilance Plan

3.1. Purpose

In the first sentence of the second paragraph of this section, we suggest that the word "might" be changed to "should", so that this sentence reads:

For products for which no special concerns have arisen, routine pharmacovigilance should be considered sufficient for post-approval safety monitoring, without the need for additional actions (e.g., safety studies).

3.2.1. Summary of ongoing safety issues

Since the Pharmacovigilance Specification would always be completed, we do not believe that the summary, taken directly from the Specification, should be repeated in the Pharmacovigilance Plan, especially if these are two parts of the same document.

3.2.2 Routine pharmacovigilance practices

The last sentence in this section should be deleted. It is not necessary to include within the Pharmacovigilance Plan a description of the company's organization and practices for conducting pharmacovigilance, especially if this is required in only some ICH regions. A statement to the effect that the company's routine pharmacovigilance practices include the elements outlined in the three bullet points in this section should be sufficient.

3.2.2. Safety action plan for specific issues/important missing information

Consistent with our previous comments, we believe the phrase "important missing information" should be deleted from the title of this section. In addition, we suggest that when defining the "objective of the proposed action", this should be expressed as an ideal or vision statement.

The last bullet, "Milestones for evaluation and reporting" should also include a description of the intended mechanism of reporting (e.g., PSUR, Periodic Report), which may be unique to the specific country regulatory requirements.

3.3.1. Design and conduct of observational studies

The second paragraph in the section includes the statement "It is recommended that the protocol be discussed with the regulatory authorities before the study starts." While we agree that regulatory authorities should have the opportunity to review and approve protocols before a study begins, we suggest that this statement be revised so that it is clear that it does not require open discussion of study protocols. In our experience, such open discussion of protocols can hamper negotiations by emphasizing details and deflecting attention from the main objective, which is obtaining agreement that the proposed study can answer the important and relevant scientific and regulatory questions.